Supplementary material

NUCLEOPHILIC RING OPENING OF BENZOXAZINONES BY DBU: SOME OBSERVATIONS

Sachin Baravkar,^a Arup Roy,^a Rupesh L. Gawade,^b Vedavati G. Puranik,^b and Gangadhar J. Sanjayan*^a

^aDivision of Organic Chemistry, ^bCenter for Materials Characterization, CSIR-National Chemical Laboratory, Pune 411008, India.

Contents	S1
General methods	S2
Experimental Section	S3-S6
Crystal Data of 13a	S7-S9
LC-MS, MALDI-TOF and HR-MS spectra of compounds	S10-S11
¹ H NMR spectra of compounds	S12-S14
¹³ C and DEPT-135 NMR spectra of compounds	S15-S21
ORTEP diagram of 13a	S22

General Methods:

Unless otherwise stated, all the chemicals and reagents were obtained commercially. Dry solvents were prepared by the standard procedures. Analytical Thin Layer Chromatography was done on pre-coated silica gel plates (Kieselgel 60F₂₅₄, Merck). Column chromatographic purifications were done with 230-400 Mesh Silica gel. NMR spectra were recorded in CDCl₃ on AV 400 MHz Bruker NMR spectrometers. All chemical shifts are reported in ppm downfield to TMS and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), and multiplet (m). Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were recorded in CHCl₃ using Shimadzu FTIR-8400 spectrophotometer. Melting points were determined on a Buchi Melting Point B-540. MALDI-TOF/TOF mass spectrum was obtained on ABSCIEX TOF/TOFTM 5800 mass spectrometer. Specific rotation measurements were carried on JASCO P2000 polarimeter. LC-MS was carried out on Thermo Finnigan Surveyor MSQ LC-MS instrument. HRMS mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

Experimental Section

Methyl-5-chloro-2-(5-chloro-2-nitrobenzamido) benzoate (3):

To a solution of 5-chloro-2-nitrobenzoic acid **1a** (0.1 g, 0.495 mmol) in DCM (10 mL) was added few drops of DMF and cooled to 0°C followed by the drop-wise addition of oxalyl chloride (0.094 g, 0.742 mmol) and the reaction mixture was kept at room temperature for 1 h. After completion of the reaction, solvent was evaporated under reduced pressure. The acid chloride formed was dissolved in 10 mL of DCM and was added drop wise to the solution of methyl-2-amino-5-chlorobenzoate **2** (0.09 g, 0.495 mmol), Et₃N (0.073 g, 0.725 mmol) in 5 mL of DCM at 0°C and the reaction mixture was kept at room temperature for 3 h. After completion of the reaction, DCM was added and the reaction mixture was washed with H₂O, KHSO₄ and NaHCO₃ respectively. The organic layer was then evaporated under reduced pressure to get the crude product which was further purified by using silica gel column chromatography to get the desired compound **3** in 61% yield. mp: 179-181°C; IR (CHCl₃) ν (cm⁻¹): 3657, 2976, 2915, 1685, 1590, 1512, 1386, 1237, 955, 847; ¹H NMR (500 MHz, CDCl₃) δ : 11.44 (s, 1H), 8.78 (d, J = 8.85 Hz, 1H), 8.11 (d, J = 8.54 Hz, 1H), 8.07 (d, J = 2.44 Hz, 1H), 7.66 (d, J = 1.83 Hz, 1H), 7.65-7.61 (m, 2H), 3.93 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ : 167.8, 163.0, 144.6, 140.7, 139.3, 134.8, 134.3, 130.9, 130.6, 128.6, 126.3, 122.2, 116.7, 52.8; LC-MS: 390.80 (M+Na)⁺; Elemental analysis calculated C₁₅H₁₀Cl₂N₂O₅ : C, 48.80; H, 2.73; N, 7.59; Found: C, 48.83; H, 2.76; N, 7.60.

6-Chloro-2-(5-chloro-2-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one (4):

3 (0.1 g, 0.271 mmol) was dissolved in 10 mL MeOH:H₂O (90:10) followed by the addition of LiOH (0.056 g, 1.355 mmol) at 0°C and reaction mixture was stirred at room temperature for 6 h. After completion of the reaction, it was treated with dil. HCl until acidic pH to get the precipitate of the product which was extracted with DCM (3 x 10 mL). The acid (0.1 g, 0.281 mmol) obtained was dissolved in DCM (10 mL) and EDC.HCl (0.052 g, 0.338 mmol) was added and reaction mixture was kept at room temperature for 1h to get the crude product

which was further purified using column chromatography (Ethyl acetate/petroleum ether, 30:70, $R_f = 0.5$) to get the compound **4** (79%, over two step) as off-white solid. mp: 196-198°C; IR (CHCl_3) $\nu(\text{cm}^{-1})$: 3657, 2977, 2891, 1767, 1600, 1385, 1255, 948, 841; ^1H NMR (400 MHz, CDCl_3) δ : 8.24 (d, $J = 2.3$ Hz, 1H), 7.99-7.96 (m, 2H), 7.83 (dd, $J = 8.2, 2.3$ Hz, 1H), 7.70 (dd, $J = 8.2, 1.8$ Hz, 1H), 7.64 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 157.0, 154.0, 146.7, 144.3, 139.6, 137.2, 135.4, 132.2, 131.0, 129.0, 128.2, 127.2, 126.0, 118.1; MALDI-TOF/TOF : 336.9192 ($\text{M}+1$)⁺; Elemental analysis calculated $\text{C}_{14}\text{H}_6\text{Cl}_2\text{N}_2\text{O}_4$: C, 49.88; H, 1.79; N, 8.31; Found: C, 49.86; H, 1.75; N, 8.29.

6-chloro-2-phenyl-4H-benzo[d][1,3]oxazin-4-one (8):

The compound **8** was prepared using known literature procedure and corresponding ^1H NMR were matched with reported products.^[1]

Tert-butyl(S)-2-((2-(methylamino)-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (11a):

The compound **11a** was prepared using known literature procedures and corresponding ^1H NMR were matched with reported products.^[2]

(S)-1-(5-chloro-2-(5-chloro-2-nitrobenzamido)benzoyl)-N-(2-(methylamino)-2-oxoethyl)pyrrolidine-2-carboxamide 12a:

Yield 72%; mp: 105-107 °C; $[\alpha]_D^{23} = + 8.706$ ($c = 0.3$, CHCl_3); IR (CHCl_3) $\nu(\text{cm}^{-1})$: 3309, 2925, 1661, 1622, 1572, 1532, 1456, 1389, 1345, 1254, 1106; ^1H NMR (400 MHz, CDCl_3) δ : 9.52 (s, 1H), 8.46 (d, $J = 9.1$ Hz, 1H), 8.06 (d, $J = 8.8$ Hz, 1H), 7.60 (d, $J = 2.1$ Hz, 1H), 7.55 (dd, $J = 8.8, 2.1$ Hz, 1H), 7.46 (dd, $J = 8.8, 2.5$ Hz, 1H); 7.32 (d, $J = 2.4$ Hz, 1H), 7.16-7.15 (m, 1H), 6.59-6.58 (m, 1H), 4.46-4.43 (m, 1H), 3.89-3.85 (m, 1H), 3.55-3.48 (m, 2H), 3.43-3.41 (m, 1H), 2.66 (d, 3H), 2.03-1.90 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 172.3, 169.0, 167.3, 164.0, 144.3, 140.5, 134.1, 133.4, 130.7, 130.5, 129.4, 127.8, 125.9, 125.7, 123.6, 60.6,

49.8, 43.0, 29.7, 29.4, 26.1, 25.1; LC-MS: 543.89 (M+Na)⁺; Elemental analysis calculated C₂₂H₂₁Cl₂N₅O₆: C, 50.59; H, 4.05; N, 13.41; Found: C, 54.56; H, 4.03; N, 13.46.

(S)-1-(2-benzamido-5-chlorobenzoyl)-N-(2-(methylamino)-2-oxoethyl)pyrrolidine-2-carboxamide 12b:

Yield 64%; mp 174-175 °C; [α]_D²³ = − 2.626 (c = 0.3, CHCl₃); IR (CHCl₃) ν (cm^{−1}): 3317, 2976, 1660, 1621, 1515, 1493, 1390, 1302, 1216; ¹H NMR (400 MHz, CDCl₃) δ: 9.63 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.48-7.43 (m, 4H), 7.18 (bs, 1H), 6.95 (bs, 1H), 4.45 (t, 1H), 4.02-3.98 (m, 1H), 3.81-3.73 (m, 2H), 3.66-3.62 (m, 1H), 2.58 (d, 2H), 2.33-2.27 (m, 2H), 2.16-2.09 (m, 2H), 1.96-1.90 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 177.7, 169.2, 168.4, 166.0, 134.9, 133.6, 132.4, 131.2, 128.7, 127.2, 126.5, 123.9, 69.5, 61.3, 53.7, 50.0, 43.1, 31.7, 29.3, 29.2, 26.0, 25.3. LC-MS: 465.5324 (M+Na)⁺; Elemental analysis calculated C₂₂H₂₃ClN₄O₄ : C, 59.66; H, 5.23; N, 12.65; Found: C, 59.62; H, 5.19; N, 12.58.

5-chloro-N-(4-chloro-2-((3-(2-oxoazepan-1-yl)propyl)carbamoyl)phenyl)-2-nitrobenzamide 13a:

Yield 20%; mp: 56-58 °C (crystallized from DCM and Pet-ether); IR (CHCl₃) ν (cm^{−1}): 3501, 1770, 1635, 1606, 1574, 1531, 1472, 1346, 1216; ¹H NMR (400 MHz, CDCl₃) δ: 12.19 (s, 1H), 8.65 (d, J = Hz, 1H), 8.46 (bs, 1H), 8.05-8.03 (d, J = 8.9 Hz, 1H), 7.80-7.79 (m, 1H), 7.65-7.64 (m, 1H), 7.56-7.54 (m, 1H); 7.48-7.47 (m, 1H), 3.50-3.48 (m, 2H), 3.36-3.32 (m, 4H), 2.58-2.56 (m, 2H), 1.75-1.73 (m, 2H), 1.72-1.68 (m, 4H), 1.66-1.64 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 177.4, 167.2, 162.8, 144.6, 140.4, 137.9, 134.6, 132.3, 130.5, 128.9, 128.7, 127.0, 126.1, 122.7, 121.5, 65.7, 49.7, 45.0, 36.9, 35.5, 29.8, 28.3, 26.8, 23.3, 15.2; HR-MS: 529.1011 (M+Na)⁺; Elemental analysis calculated for C₂₃H₂₄Cl₂N₄O₅ : C, 54.45; H, 4.77; N, 11.04; Found: C, 54.51; H, 4.71; N, 11.08

2-benzamido-5-chloro-N-(3-(2-oxazepan-1-yl)propyl) benzamide 13b:

Yield 13%; mp 68-70 °C; IR (CHCl₃) δ (cm⁻¹) : 3306, 2927, 2855, 1720, 1669, 1645, 1352, 1301, 1199; ¹H NMR (400 MHz, CDCl₃) δ : 12.44 (s, 1H), 8.76 (d, J = 9.0 Hz, 1H), 8.28 (bs, 1H), 7.98-7.95 (m, 1H), 7.73 (d, J = 2.3 Hz, 1H), 7.47-7.39 (m, 4H), 3.47-3.44 (m, 2H), 3.38-3.29 (m, 4H), 2.54-2.52 (m, 2H), 1.71-1.60 (m, 8H). ¹³C NMR (100 MHz, CDCl₃) δ : 177.6, 167.9, 165.5, 138.8, 134.8, 132.3, 131.7, 128.7, 127.3, 127.0, 122.5, 121.5, 49.7, 45.1, 37.0, 35.5, 29.9, 28.4, 27.0, 23.3 ; HR-MS: 428.1731 (M+H)⁺; Elemental analysis calculated for C₂₃H₂₆ClN₃O₃ : C, 64.55; H, 6.12; N, 9.82; Found: C, 64.50; H, 6.15; N, 9.87.

-
- [1] Lian, X. L.; Lei, H.; Quan, X. J.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Chem. Commun.* **2013**, 49, 8196-8198.
- [2] (a) Tonan, K.; Ikawa, S. *Spectrochim. Acta Mol. Biomol. Spectros.* **2003**, 59, 111-120. (b) Stimson, E. R.; Zimmerman, S. S.; Scheraga, H. A. *Macromolecules* **1977**, 10, 1049-1060.

Crystal Data of compound 13a:

Single crystals of the complex were grown by slow evaporation of the solution mixture of DCM and Pet-ether. Data was collected on SMART APEX-II CCD using Mo-K α radiation ($\lambda = 0.7107 \text{ \AA}$) to a maximum θ range of 25.00° . Colourless plate like crystal of approximate size $0.47 \times 0.26 \times 0.09 \text{ mm}^3$ was used for data collection. Crystal to detector distance 5.00 cm, 512×512 pixels / frame, Oscillation / frame - 0.5° , maximum detector swing angle = -30.0° , beam centre = (260.2, 252.5), in plane spot width = 1.24, Multi-run data acquisition. Total scans = 2, total frames = 721, exposure / frame = 5.0 sec / frame, θ range = 2.22 to 25.00° , completeness to θ of 25.00° , is 99.7 %. $\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_5$, $M = 507.36$. Crystals belong to Monoclinic, space group $P2_1/n$, $a = 10.2854(2)$, $b = 9.9221(2)$, $c = 23.8491(5) \text{ \AA}$, $V = 2427.19(8) \text{ \AA}^3$, $Z = 4$, $D_c = 1.388 \text{ g /cc}$, $\mu (\text{Mo-K}\alpha) = 0.309 \text{ mm}^{-1}$, 10608 reflections measured, 4257 unique [$I > 2\sigma(I)$], R value 0.0426, $wR2 = 0.1069$. Largest diff. peak and hole 0.332 and $-0.269 \text{ e. \AA}^{-3}$. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2 . Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in table 1.

The conformation of the molecule was established by single crystal X-ray analysis.

Table S1. Crystal data and structure refinement for $\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_5$ compound **13a**

Empirical formula	$\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_5$
Formula weight	507.36
Temperature	296 K
Wavelength	$0.71073 \text{ \AA}$
Crystal system	Monoclinic

Space group	P21/n	
Unit cell dimensions	a = 10.2854(2) Å	$\alpha = 90^\circ$.
	b = 9.9221(2) Å	$\beta = 94.244(1)^\circ$.
	c = 23.8491(5) Å	$\gamma = 90^\circ$.
Volume	2427.19(8) Å ³	
Z	4	
Density (calculated)	1.388 g/cc	
Absorption coefficient	0.309 mm ⁻¹	
F(000)	1056	
Crystal size	0.47 x 0.26 x 0.09 mm ³	
Theta range for data collection	2.22 to 25.00°.	
Index ranges	-12 ≤ h ≤ 12, -11 ≤ k ≤ 10, -25 ≤ l ≤ 28	
Reflections collected	10608	
Independent reflections	4257 [R(int) = 0.0389]	
Completeness to theta = 25.00°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9727 and 0.8670	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4257 / 0 / 308	
Goodness-of-fit on F ²	1.032	
Final R indices [I > 2sigma(I)]	R1 = 0.0426, wR2 = 0.1069	
R indices (all data)	R1 = 0.0568, wR2 = 0.1176	
Extinction coefficient	0.0101(10)	
Largest diff. peak and hole	0.332 and -0.269 e.Å ⁻³	

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å² × 10³) for sachinsanj_0m. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	7939(1)	-2429(1)	7754(1)	110(1)
Cl(2)	3096(1)	4688(1)	10434(1)	85(1)
O(1)	6759(2)	-123(2)	10382(1)	63(1)
O(2)	5047(2)	2437(1)	8783(1)	65(1)
O(3)	943(2)	4440(2)	7860(1)	68(1)

O(4)	8811(2)	1796(2)	10642(1)	81(1)
O(5)	8590(2)	2060(2)	11522(1)	93(1)
N(1)	6411(2)	1115(2)	9578(1)	47(1)
N(2)	4173(2)	1114(2)	8096(1)	57(1)
N(3)	129(2)	2521(2)	8184(1)	51(1)
N(4)	8188(2)	2122(2)	11030(1)	57(1)
C(1)	6471(2)	921(2)	10140(1)	44(1)
C(2)	6714(2)	198(2)	9160(1)	42(1)
C(3)	6120(2)	355(2)	8617(1)	44(1)
C(4)	6507(2)	-467(2)	8189(1)	56(1)
C(5)	7441(2)	-1446(2)	8300(1)	60(1)
C(6)	7997(2)	-1628(2)	8836(1)	57(1)
C(7)	7640(2)	-808(2)	9265(1)	50(1)
C(8)	5069(2)	1396(2)	8502(1)	48(1)
C(9)	3020(2)	1926(2)	7961(1)	55(1)
C(10)	1853(2)	1009(2)	7866(1)	62(1)
C(11)	586(2)	1754(3)	7716(1)	68(1)
C(12)	331(2)	3846(2)	8211(1)	48(1)
C(13)	-177(3)	4611(2)	8687(1)	67(1)
C(14)	547(3)	4318(3)	9252(1)	78(1)
C(15)	101(3)	3057(3)	9533(1)	80(1)
C(16)	260(3)	1788(3)	9198(1)	70(1)
C(17)	-489(2)	1773(3)	8624(1)	68(1)
C(18)	6094(2)	2156(2)	10454(1)	42(1)
C(19)	6875(2)	2676(2)	10904(1)	46(1)
C(20)	6516(2)	3761(2)	11211(1)	59(1)
C(21)	5343(3)	4390(2)	11071(1)	63(1)
C(22)	4557(2)	3893(2)	10625(1)	55(1)
C(23)	4909(2)	2784(2)	10322(1)	50(1)

Mass Spectra of 3, 4, 8, 12a, 12b, 13a and 13b

MALDI-TOF/TOF

LC-MS

NBAPG_130827151109 #9-20 RT: 0.14-0.33 AV: 12 SB: 36 0.00-0.12 , 0.33-0.80 NL: 3.95E6
T: {0,0} + c ESI corona sid=75.00 det=1600.00 Full ms [100.00-2000.00]

LC-MS

HR-MS

AADBU_120626150022 #1-17 RT: 0.01-0.20 AV: 17 NL: 1.70E6
T: FTMS + p ESI Full ms [200.00-800.00]

PHADBU_120626145705 #1-18 RT: 0.01-0.21 AV: 18 NL: 3.84E6
T: FTMS + p ESI Full ms [200.00-800.00]

HR-MS

^1H NMR (500 MHz, CDCl_3)

^1H NMR (500 MHz, CDCl_3)

i5ECX400#011_PROTON-3.jdf

^1H NMR (400 MHz, CDCl_3)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

DEPT-135 NMR (100 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

DEPT-135 NMR (100 MHz, CDCl_3)

ri5ECX400#011_DEPT135-3.jdf

^{13}C NMR (100 MHz, CDCl_3)

DEPT-135 (100 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

DEPT-135 (100 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

DEPT-135 (100 MHz, CDCl_3)

2DBUDPT.ESP

^{13}C NMR (100 MHz, CDCl_3)

DEPT-135 (100 MHz, CDCl_3)

hu5av500#065.002.001.1r.esp

Fig S1: ORTEP diagram of oligomer **13a**